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# Malnutrition (Subjective Global Assessment) scores and serum albumin levels, but not body mass Index values, at initiation of dialysis are independent predictors of mortality: A 10-year clinical cohort study

Maria Chan

*University of Wollongong, [mcf560@uow.edu.au](mailto:mcf560@uow.edu.au)*

J Kelly

*University of New South Wales, Sydney, Australia, St. George Hospital*

Marijka Batterham

*University of Wollongong, [marijka@uow.edu.au](mailto:marijka@uow.edu.au)*

Linda Tapsell

*University of Wollongong, [ltapsell@uow.edu.au](mailto:ltapsell@uow.edu.au)*

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# Malnutrition (Subjective Global Assessment) scores and serum albumin levels, but not body mass Index values, at initiation of dialysis are independent predictors of mortality: A 10-year clinical cohort study

## Abstract

**OBJECTIVE:** To examine the associations between demographic, clinical, lifestyle, and nutritional parameters at the start of dialysis and mortality, including the combined effects on nutritional parameters, which were seldom investigated in the literature. **DESIGN:** Ten-year retrospective clinical cohort study. **SETTING:** Dialysis unit of a metropolitan tertiary teaching hospital in Sydney, Australia. **SUBJECTS:** Incident dialysis patients (n = 167; hemodialysis, 57.5%; male, 61.7%; age, 65.3 ± 13.6 years; diabetic, 24.5%) who commenced on a planned dialysis program. **METHODS:** Associations were examined between all-cause mortality and baseline demographics, including age and gender; clinical and lifestyle characteristics, including glomerular filtration rate, smoking habits, presence of comorbidities (e.g., coronary artery disease, diabetes mellitus, and peripheral vascular disease); and nutritional parameters, including body mass index (BMI), serum albumin (s-albumin) levels, and subjective global assessment score (SGA). Associations with combination values for malnutrition, s-albumin (65 years, P < .0001), presence of peripheral vascular disease (P < .0001), reduced s-albumin levels (P = .01), and malnutrition scores (P = .02) independently predicted mortality. Being overweight and obese (BMI: ≥26 kg/m<sup>2</sup>) did not show any advantage on survival (P = .73). Being malnourished and overweight (or obese) was associated with a 3-fold increase in mortality risk (adjusted hazard ratio [HR], 2.96; 95% confidence interval [CI], 1.12 to 7.33; P = .02) compared with being well nourished with a BMI <26 kg/m<sup>2</sup> (referent). Compared with being well nourished (SGA = A), being malnourished with normal or low s-albumin was associated with higher risk (HR, 2.06; 95% CI, 1.06 to 4.00; P = .03 and HR, 2.86; 95% CI, 1.65 to 4.94; P < .0001, respectively). There was no statistical difference between mortality risks through any combination of s-albumin and BMI values (P = .54). **CONCLUSION:** Malnutrition and reduced s-albumin levels were found to be independent predictors of mortality, whereas being overweight and obese did not show protective effects.

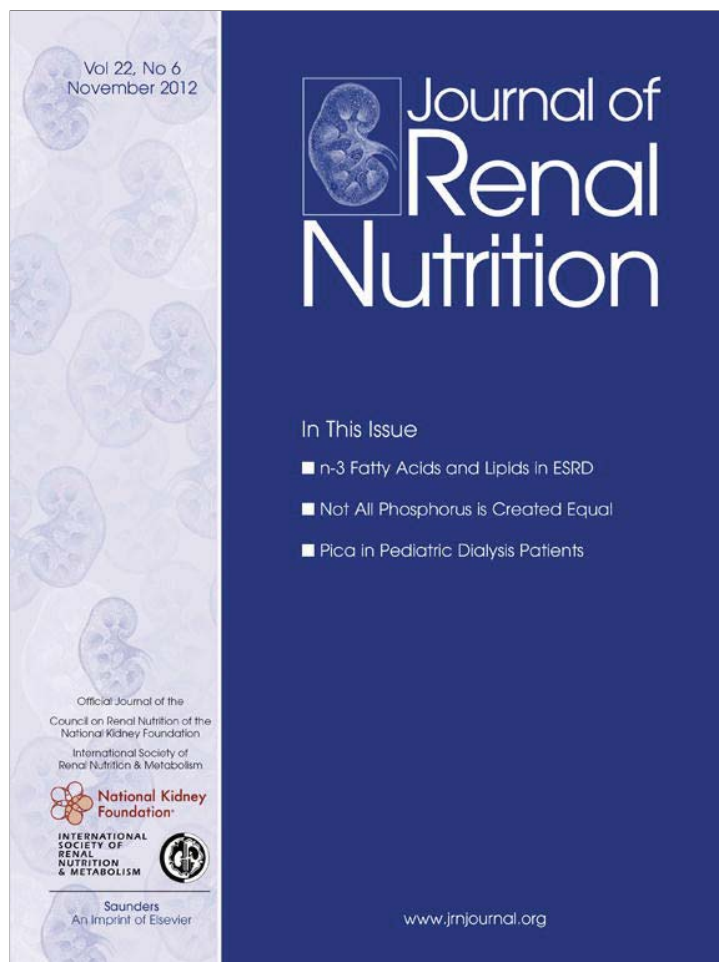
## Keywords

albumin, index, values, initiation, dialysis, independent, predictors, mortality, 10, serum, scores, but, assessment, levels, global, subjective, malnutrition, not, year, clinical, mass, cohort, body, study

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## ORIGINAL RESEARCH

# **CPE** Malnutrition (Subjective Global Assessment) Scores and Serum Albumin Levels, but not Body Mass Index Values, at Initiation of Dialysis are Independent Predictors of Mortality: A 10-Year Clinical Cohort Study

Maria Chan, BSc(Hons), MNutrDiet, GradDip ExSpSc, AdvAPD,\*†‡  
 John Kelly, MBBS, MD,‡§ Marijka Batterham, MSc(Nutr&Diet), MMedStat, PhD,  
 GStat, AdvAPD,¶ and Linda Tapsell, PhD, FDAA†

**Objective:** To examine the associations between demographic, clinical, lifestyle, and nutritional parameters at the start of dialysis and mortality, including the combined effects on nutritional parameters, which were seldom investigated in the literature.

**Design:** Ten-year retrospective clinical cohort study.

**Setting:** Dialysis unit of a metropolitan tertiary teaching hospital in Sydney, Australia.

**Subjects:** Incident dialysis patients (n = 167; hemodialysis, 57.5%; male, 61.7%; age, 65.3 ± 13.6 years; diabetic, 24.5%) who commenced on a planned dialysis program.

**Methods:** Associations were examined between all-cause mortality and baseline demographics, including age and gender; clinical and lifestyle characteristics, including glomerular filtration rate, smoking habits, presence of comorbidities (e.g., coronary artery disease, diabetes mellitus, and peripheral vascular disease); and nutritional parameters, including body mass index (BMI), serum albumin (s-albumin) levels, and subjective global assessment score (SGA). Associations with combination values for malnutrition, s-albumin (<3.3 vs. ≥3.3 g/dL), and BMI (<26 vs. ≥26 kg/m<sup>2</sup>) were also examined.

**Results:** Median survival was 54.2 months (interquartile range, 23 to 83), and 52.1% of patients were malnourished (SGA score B and C) at the start of dialysis. Advanced age (classified as >65 years,  $P < .0001$ ), presence of peripheral vascular disease ( $P < .0001$ ), reduced s-albumin levels ( $P = .01$ ), and malnutrition scores ( $P = .02$ ) independently predicted mortality. Being overweight and obese (BMI: ≥26 kg/m<sup>2</sup>) did not show any advantage on survival ( $P = .73$ ). Being malnourished and overweight (or obese) was associated with a 3-fold increase in mortality risk (adjusted hazard ratio [HR], 2.96; 95% confidence interval [CI], 1.12 to 7.33;  $P = .02$ ) compared with being well nourished with a BMI <26 kg/m<sup>2</sup> (referent). Compared with being well nourished (SGA = A), being malnourished with normal or low s-albumin was associated with higher risk (HR, 2.06; 95% CI, 1.06 to 4.00;  $P = .03$  and HR, 2.86; 95% CI, 1.65 to 4.94;

\*Department of Nutrition and Dietetics, St. George Hospital, Sydney, New South Wales, Australia.

†Nutrition Research, Illawarra Health and Medical Research Institute, School of Health Sciences, University of Wollongong, Wollongong, New South Wales, Australia.

‡St. George Clinical School, School of Medicine, University of New South Wales, Sydney, Australia.

§Department of Renal Medicine, St. George Hospital, Sydney, New South Wales, Australia.

¶Centre for Statistical and Survey Methodology, University of Wollongong, Wollongong, New South Wales, Australia.

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Address reprint requests to Maria Chan, BSc(Hons), MNutrDiet, GradDip ExSpSc, AdvAPD, Department of Nutrition and Dietetics, St. George Hospital, Gray Street, Kogarah, New South Wales 2217, Australia. E-mail: maria.chan@sesiahs.health.nsw.gov.au

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$P < .0001$ , respectively). There was no statistical difference between mortality risks through any combination of s-albumin and BMI values ( $P = .54$ ).

**Conclusion:** Malnutrition and reduced s-albumin levels were found to be independent predictors of mortality, whereas being overweight and obese did not show protective effects.

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**P**ROTEIN ENERGY WASTING and poor nutritional status are common in patients with end-stage kidney disease (ESKD) on maintenance dialysis.<sup>1-3</sup> These are strong predictors of mortality and morbidity and are associated with poor quality of life.<sup>4,5</sup> Factors affecting nutrition in uremic patients include (1) disturbance of energy, protein, and nutrients metabolism,<sup>6</sup> (2) metabolic acidosis,<sup>7</sup> (3) anorexia, taste change, and poor appetite that may lead to suboptimal dietary intake,<sup>8-10</sup> (4) dialysis procedures *per se*,<sup>4</sup> such as biocompatibility, inadequate dialysis, protein and other nutrient losses, and peritoneal dialysis (PD) dialysate-induced glucose loading and sense of fullness,<sup>11</sup> (5) hormonal derangement,<sup>12</sup> (6) comorbidities, such as cardiovascular disease and diabetes mellitus, (7) infection and intercurrent illnesses, (8) chronic inflammation,<sup>2</sup> (9) altered muscle metabolism<sup>13</sup> and physical inactivity,<sup>14</sup> (10) loss of residual renal function,<sup>15</sup> (11) psychosocial issues<sup>16</sup> and poor food management skill, and (12) conditions associated with various stages of lifecycle that require additional nutritional attention, such as menopause, aging-related sarcopenia, and poor dentition. Many of these nutrition abnormalities emerge during the progressive decline of renal function before dialysis is required.<sup>8,17</sup>

In the dialysis population, nutritional factors found to predict mortality risk are anthropometric measures, such as low weight-to-height ratio,<sup>18</sup> low body mass index (BMI), and unintentional weight loss<sup>19</sup>; abnormal laboratory results, such as high level of C-reactive protein (CRP)<sup>20</sup> and low levels of lymphocytes, parathyroid hormone, serum albumin, prealbumin, and hemoglobin<sup>19,21-25</sup>; poor appetite,<sup>26</sup> muscle wasting,<sup>27</sup> suboptimal intakes of energy and protein,<sup>9</sup> low exercise capacity,<sup>14</sup> and poor functional capacity measured by hand grip strength<sup>27</sup>; and malnutrition score using subjective global assessment (SGA).<sup>28</sup> Many of these abnormalities present at the start of dialysis and predicted poor outcomes.<sup>4,27,28</sup> However, there has been

much debate on the prognostic significance of s-albumin-CRP,<sup>28,29</sup> BMI,<sup>30-33</sup> and timing of initiation of dialysis.<sup>34,35</sup> It is necessary to understand the relationships between mortality and these modifiable factors so that predialysis intervention can be considered to improve outcomes. The aims of the present study were (1) to describe the demographic, clinical, and nutritional characteristics in a cohort of ESKD patients who commenced on planned dialysis program in our unit, (2) to examine the associations between these factors and mortality, and (3) to examine the combined effects of nutritional factors on mortality risk, as these methods were seldom investigated in the previous studies.

## Patients and Methods

This was a retrospective clinical cohort study involving all incident hemodialysis (HD) and PD patients at the renal unit of The George Hospital, Sydney, Australia, between August 1, 2000 and July 31, 2005. All patients were followed until death, or they were censored at transplant or at the end of the observational period on July 31, 2010. This means all patients completed at least 5 years of follow-up during the 10-year study period. Inclusion criteria were ESKD patients who were older than 18 years and who commenced a planned dialysis program after gradual decline of renal function without history of acute kidney injury (AKI) and renal replacement therapy (RRT). Initiation of dialysis was recommended by the patients' primary nephrologists based on clinical judgments (e.g., when glomerular filtration rate [GFR] was  $<7$  mL/minutes/1.73 m<sup>2</sup> or indication of uncontrolled uremic symptoms such as volume overload). Exclusion criteria were patients in whom dialysis was initiated because of AKI with or without recovering renal function, previous history of RRT, planned early discontinuation of dialysis program from our unit (e.g., living donor transplantation or transfer

to another unit), and incomplete assessment by the dietitian within 4 weeks of dialysis initiation.

Clinical and demographic data extracted from the hospital clinical notes and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) included age; gender; race; smoking history (never smoked or combined ex- and current smokers); late referral to nephrologists, defined as <3 months under specialist care before starting dialysis; and comorbidities, such as coronary artery disease (CAD), cerebral vascular disease (CVD), diabetes mellitus (DM), chronic lung disease (CLD), and peripheral vascular disease (PVD). ANZDATA classified the presence of comorbidity as "yes," "suspected," or "no"; data of "yes" and "suspected" were combined as "presence of" for analysis in this study. Mortality and cause of death were also extracted.

In line with the clinical guidelines,<sup>36</sup> which are based on the latest best evidence and expert opinion, if a high level of evidence did not exist or was inconclusive, all patients were assessed by the renal unit dietitians, including the author M.C., as part of the routine care. Anthropometric measures included for analysis were height (m), edema-free body weight (kg), BMI = weight ÷ height<sup>2</sup> (m/kg<sup>2</sup>), and weight history (in particular if any unintentional weight loss occurred in the previous 6 months for SGA rating). The previous routine blood results before the first dialysis session were extracted from clinical notes. These included s-albumin (reference range, 3.3 to 5.3 g/dL) and serum creatinine results to calculate GFR using the Cockcroft-Gault equation. The survival risk between the early and late starting groups was compared using the Initiating Dialysis Early and Late (IDEAL) trial intended cutoff of  $\geq 7$  and  $< 7$  mL/minutes/1.73 m<sup>2</sup> as early and late initiation, respectively<sup>37</sup>; further analyses were performed at cutoffs of 8, 9, and 10 mL/minutes/1.73 m<sup>2</sup>. To eliminate the negative effect of acute-phase response of s-albumin due to the insertion of PD catheter, the most recent s-albumin readings before the procedures were used. Other assessment performed by the renal dietitian(s) was SGA,<sup>38</sup> which categorizes patients as A = well nourished, B = mild-moderately malnourished, and C = severely malnourished, based on the patient's medical history and physical examination. Urea kinetic studies were routinely performed for all patients throughout the study period to meet the optimal national dialysis targets.<sup>39</sup> The clinical practice

guidelines<sup>36</sup> define healthy range for BMI as 22 to 26 kg/m<sup>2</sup>; we considered BMI  $\geq 26$  kg/m<sup>2</sup> as obese or overweight. Additional analyses were performed according to the World Health Organization-defined categories<sup>40</sup> of underweight, healthy weight range, overweight, and obese (BMI: <18.5, 18.5 to 25.0, 25 to 30, and  $\geq 30$  kg/m<sup>2</sup>, respectively) as well as renal-specific BMI categories<sup>36,41</sup> of undernourished, ideal range, overweight, and obese (BMI: <23, 23 to 26, 26 to 30, and  $\geq 30$  kg/m<sup>2</sup>, respectively). The combined effects of malnutrition (classified by SGA score B or C), s-albumin (<3.3 vs.  $\geq 3.3$  g/dL), and BMI (<26 vs.  $\geq 26$  kg/m<sup>2</sup>) were also examined. For example, the combined effects of SGA and BMI were determined using the following forms of categorization: group 1 (SGA = A + BMI: <26 kg/m<sup>2</sup>), group 2 (SGA = A + BMI:  $\geq 26$  kg/m<sup>2</sup>), group 3 (SGA = B and C + BMI: <26 kg/m<sup>2</sup>), and group 4 (SGA = B and C + BMI:  $\geq 26$  kg/m<sup>2</sup>). Similar forms of categorization applied to SGA and s-albumin as well as s-albumin and BMI combinations.

All tests were performed using the statistical software SPSS version 18 (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean  $\pm$  standard deviation for normally distributed data and as medians with interquartile ranges for non-normally distributed data. For continuous variables, comparisons between groups were performed using unpaired sample *t* test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables, whereas categorical variables were compared using the  $\chi^2$  test. Survival analysis was performed using the Kaplan-Meier method (univariate analysis), and Cox proportional hazard analysis (multivariate analysis) was used to assess the independent association between baseline parameters and mortality. Effect of age (>65 years), GFR (<7 mL/minutes/1.73 m<sup>2</sup>), s-albumin (<3.3 g/dL), and BMI ( $\geq 26$  and  $\geq 30$  kg/m<sup>2</sup>) as continuous and categorical variables were also examined.  $P < .05$  was considered to be statistically significant.

The study was approved by the ethics committee of the South Eastern Sydney and Illawarra Area Health Service, NSW, Australia.

## Results

Dialysis was initiated in 330 patients in the defined period. Of these, 167 patients (50.6%) met

the inclusion criteria. One hundred sixty-three patients (49.4%) were excluded from analysis because of AKI with or without recovering renal function (32.8%), previous history of RRT (2.1%), planned early discontinuation of dialysis program from our unit (10.3%), and other causes (e.g., <18 years of age, incomplete dietitian assessment within 4 weeks of enrollment, or missing data; 4.2%). The mean age ( $\pm$  standard deviation) of the studied subjects was  $65.3 \pm 13.6$  years (male, 61.7%). Of these patients, 57.5% were on HD and the rest were on PD at day 90 after enrollment; 64 patients (38.3%) switched dialysis modality during the study period. Similar survival rates were reported in the literature for both modalities<sup>28,42</sup> even after switching from one to the other.<sup>43</sup> As we found similar results by the Kaplan-Meier analysis ( $P = .89$ ), all HD and PD data were combined for analysis. Twenty-eight patients (16.8%) received a kidney transplant after entry to the study.

The baseline demographic, clinical, and nutritional characteristics of the studied patients at the initiation of dialysis are listed in Table 1.

Late referral (<90 days) to the nephrologists was noted in 8.5% of patients, and dialysis was commenced with a mean GFR of  $8.0 \pm 2.7$  mL/minutes/1.73 m<sup>2</sup>. Apart from body weight and serum creatinine, there was no statistical difference between male and female patients for all other demographic, clinical, and nutritional parameters. In all, 111 patients (66.6%) died, including 2 of the transplanted patients, by the end of the observation period. Three patients were transferred to other hospitals, but their survival data were obtained from the ANZDATA for analysis. Median follow-up time was 53.0 (interquartile range, 23 to 83) months, with 96.5 (76.3 to 108.8) versus 29 (17.0 to 53.0) months for survivors and non-survivors, respectively. The causes of ESKD and death are listed in Table 2. The main cause of ESKD was diabetic nephropathy (24%). The most common cause of death was withdrawal of dialysis due to refusal and quality of life measures (21.6%).

Among the patients studied, dialysis was initiated early in 37.2% ( $\geq 7$  mL/minutes/1.73 m<sup>2</sup>) and late in 62.8% (<7 mL/minutes/1.73 m<sup>2</sup>),

**Table 1.** Demographic, Clinical, and Nutritional Characteristics of the Studied Subjects at Baseline

Parameters	Total	Male	Female
Number (%)	167	103 (61.7%)	64 (38.3%)
Demographics			
Age (year)	65.3 $\pm$ 13.6	65.8 $\pm$ 13.9	64. $\pm$ 13.1
Race, white (%)	83.3	83.5	82.8
Clinical and comorbidities			
Hemodialysis at 3 month (%)	57.5	62.1	50.0
Serum creatinine ( $\mu$ mol/L)	800.6 $\pm$ 288.1	867.4 $\pm$ 314.4	683.0 $\pm$ 199.3*
Glomerular filtration rate (mL/minutes/1.73 m <sup>2</sup> )	8.0 $\pm$ 2.7	7.8 $\pm$ 2.7	8.2 $\pm$ 2.7
Late referral† (%)	8.5	10.6	4.7
Smoking (positive history)‡ (%)	43.7	47.3	35.0
Chronic lung disease§ (%)	15.8	15.5	16.4
Coronary artery disease¶ (%)	46.2	48.5	42.6
Peripheral vascular disease** (%)	24.5	24.5	24.6
Cerebral vascular disease†† (%)	23.9	22.4	26.3
Diabetes mellitus (%)	33.5	34	32.8
Nutritional			
Serum albumin (g/dL)	3.1 $\pm$ 0.5	3.1 $\pm$ 0.5	3.2 $\pm$ 0.5
Weight (kg)	69.5 $\pm$ 17.1	73.6 $\pm$ 14.5	62.8 $\pm$ 18.9*
Body mass index (kg/m <sup>2</sup> )	25.9 $\pm$ 6.9	25.9 $\pm$ 4.4	25.9 $\pm$ 7.7
Malnourished, subjective global assessment score B and C (%)	52.1	48.5	57.8

$P$  value is for comparison of the gender groups.

\* $P < .0001$ .

†Data missing in 2 patients.

‡Data missing in 10 patients.

§Data missing in 9 patients.

¶Data missing in 9 patients.

\*\*Data missing in 9 patients.

††Data missing in 9 patients.

**Table 2.** Causes of End-Stage Kidney Disease and Mortality

Causes	%
Causes of end-stage kidney disease (n = 167)	
Chronic glomerulonephritis	21.6
Diabetic nephropathy	24.0
Renovascular disease/hypertensive nephrosclerosis	18.6
Adult polycystic kidney disease	5.4
Analgesic nephropathy	9.6
IgA nephropathy	6.0
Reflux nephropathy/congenital abnormality	4.8
Other or unknown causes	9.0
Causes of death (n = 111)	
Myocardial infarction	9.0
Cardiovascular accident	1.8
Cardiac arrest	11.7
Sepsis/infection	15.3
Other causes and illnesses	18.0
Withdrawal due to:	
Refusal/quality of life measures	21.6
Cerebrovascular comorbidities	12.6
Peripheral vascular comorbidities	4.5
Malignancy	2.7
Unknown causes	2.7

with a mean GFR of  $9.4 \pm 2.2$  versus  $5.5 \pm 1.0$  mL/minutes/1.73 m<sup>2</sup>, respectively;  $P < .0001$ . The early-start group in comparison with the

late-start group had significantly higher BMI ( $27.5 \pm 6.3$  vs.  $23.3 \pm 3.9$  kg/m<sup>2</sup>,  $P < .0001$ ) and included fewer malnourished patients (43.8% vs. 66.1%,  $\chi^2 = 7.8$ ,  $P = .005$ ). There was no statistical difference between the 2 groups for all other variables. Kaplan–Meier analysis showed no statistical difference in mortality between the 2 groups ( $P = .79$ ). Further analysis did not show any statistical difference in mortality between the early- versus late-start groups, with the GFR cutoff of 8 mL/minutes/1.73 m<sup>2</sup> ( $10.2 \pm 1.2$  vs.  $6.1 \pm 2.2$ ),  $P < .0001$ ; 9 mL/minutes/1.73 m<sup>2</sup> ( $11.1 \pm 1.5$  vs.  $6.6 \pm 2.1$ ),  $P < .0001$ ; or 10 mL/minutes/1.73 m<sup>2</sup> ( $12.0 \pm 1.6$  vs.  $6.9 \pm 2.1$ ),  $P < .0001$ . Our data indicated that GFR levels at which dialysis started were not found to have any association with mortality risk.

Among the lifestyle and comorbidity parameters, PVD was independently associated with higher mortality risk ( $P < .0001$ ), whereas the significance of CAD disappeared in the adjusted analyses ( $P = .10$ ). Smoking and all other comorbidities did not show any statistically significant effect on mortality risks (Table 3).

Fifty-eight percent of patients had s-albumin levels  $< 3.3$  g/dL (reference range, 3.3 to 5.3 g/dL). The low-s-albumin group, when compared

**Table 3.** Cox Proportional Hazards Analysis (Multivariate Model) of Factors Affecting Morality

Parameters	Unadjusted Hazard Ratios (95% Confidence Interval)	P Value	Adjusted Hazard Ratios (95% Confidence Interval)*	P Value
Age (per year increase)	1.08 (1.05-1.11)	$< .0001$	1.08 (1.05-1.12)	$< .0001$
Age ( $> 65$ years)	2.76 (1.51-5.06)	$< .001$	3.06 (1.70-5.51)	$< .0001$
Gender (male)	1.31 (0.84-2.04)	NS (0.23)	1.33 (0.86-2.06)	NS (0.20)
Glomerular filtration rate (per mL/minutes increase)	1.09 (0.98-1.21)	NS (0.10)	1.07 (0.97-1.17)	NS (0.10)
Hemodialysis	0.67 (0.43-1.06)	NS (0.09)	0.75 (0.48-1.16)	NS (0.19)
s-albumin (per g/dL increase)	0.92 (0.87-0.98)	.01	0.93 (0.89-0.98)	.01
s-albumin ( $< 3.3$ g/dL)	1.60 (0.95-2.71)†	.08	1.86 (1.17-2.97)†	.01
Body mass index (per kg increase)	0.97 (0.92-1.03)	NS (0.30)	0.97 (0.92-1.03)	NS (0.30)
Body mass index ( $\geq 30$ kg/m <sup>2</sup> )	0.68 (0.36-1.29)	NS (0.23)	0.67 (0.36-1.27)	NS (0.22)
Body mass index ( $\geq 26$ kg/m <sup>2</sup> )	0.91 (0.52-1.59)	NS (0.73)	0.91 (0.52-1.59)	NS (0.73)
Malnourished, subjective global assessment score B and C	1.76 (1.01-3.05)	.046	1.74 (1.11-2.72)	.02
Smoking (positive history)	1.46 (0.95-2.23)	NS (0.09)	1.45 (0.96-2.19)	NS (0.08)
Chronic lung disease	0.85 (0.50-1.45)	NS (0.56)	0.86 (0.50-1.45)	NS (0.56)
Coronary artery disease	1.71 (1.04-2.81)	.04	1.45 (0.94-2.19)	NS (0.10)
Peripheral vascular disease	2.62 (1.57-4.37)	$< .0001$	2.42 (1.57-3.73)	$< .0001$
Cerebral vascular disease	1.01 (0.61-1.67)	NS (0.98)	1.01 (0.61-1.67)	NS (1.01)
Diabetes mellitus	1.10 (0.68-1.75)	NS (0.71)	1.09 (0.69-1.74)	NS (0.71)

NS, nonsignificant.

\*Analysis with age as categorical variable unless stated otherwise. Hazard ratio adjusted for all other variables including age, gender, dialysis modality, s-albumin, body mass index, subjective global assessment, smoking, and all co-morbidities.

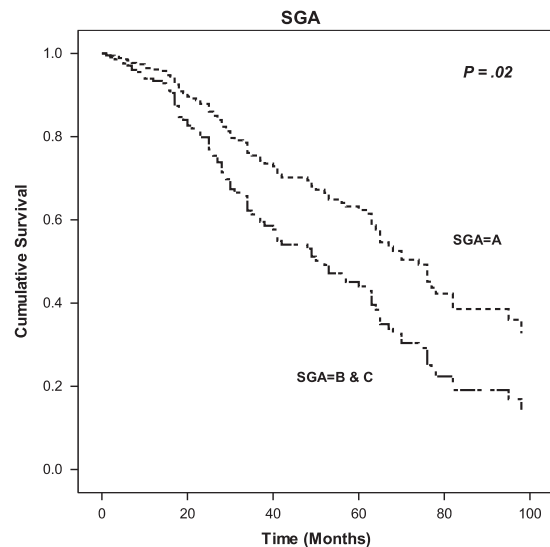
†Analysis with age as continuous variable.



with patients with normal s-albumin levels, had significantly lower s-albumin ( $2.8 \pm 0.3$  vs.  $3.5 \pm 0.3$  g/dL,  $P < .0001$ ), lower GFR ( $7.3 \pm 2.3$  vs.  $8.8 \pm 2.9$  mL/minutes/1.73 m<sup>2</sup>,  $P < .0001$ ), and higher prevalence of malnutrition (66.3% vs. 34.2%,  $\chi^2 = 16.9$ ,  $P < .0001$ ). There was no statistical difference between the 2 groups for all other variables. Cox proportional hazard model revealed that the measure of s-albumin, as both a continuous and categorical variable, was independently associated with survival;  $P = .01$  and  $.01$ , respectively (Table 3).

More than half of the patients (55.1%) were overweight or obese (BMI:  $\geq 26$  kg/m<sup>2</sup>), and 17.4% of patients were obese (BMI:  $\geq 30$  kg/m<sup>2</sup>). Kaplan-Meier analysis indicated no statistical difference in mortality risk between patients with BMI  $< 26$  and  $\geq 26$  kg/m<sup>2</sup> (overweight and obese),  $P = .08$  and  $< 30$  or  $\geq 30$  kg/m<sup>2</sup> (obese) groups,  $P = .11$ . After adjusting for all other variables, Cox proportional hazards analysis indicated similar effects ( $P = .73$  and  $0.22$ , respectively; Table 3). Kaplan-Meier analysis showed no statistical difference in mortality between the 4 World Health Organization BMI categories<sup>40</sup> ( $P = .26$ ) nor among the renal-specific BMI categories ( $P = .72$ ).<sup>36,41</sup>

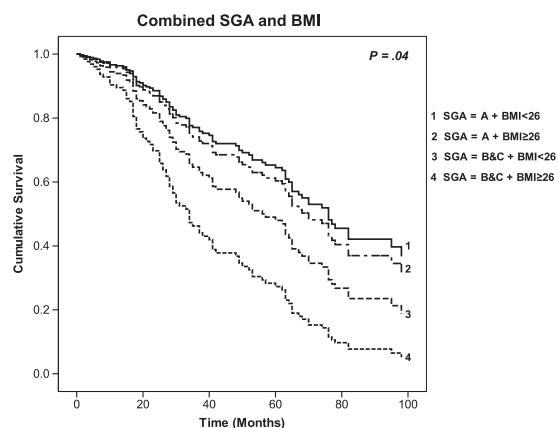
Within the cohort, 47.9%, 41.9%, and 10.2% of patients were rated as well nourished (SGA = A), mildly to moderately malnourished (SGA = B), and severely malnourished (SGA = C), respectively. Kaplan-Meier analysis indicated a significant difference in the mortality risk between the 3 groups ( $P < .0001$ ). After adjusting for all other variables using the Cox proportional hazard model, the survival curves of SGA B and C merged, and the combined malnourished group (SGA = B and C, 52.1%) showed significantly higher mortality risk compared with the well-nourished group (SGA = A) (adjusted hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.11 to 2.72;  $P = .02$ ; Table 3 and Fig. 1). Therefore, malnutrition was found independently associated with mortality. It is worth noting that the well-nourished group had significantly more diabetic patients than the malnourished group (41.4% vs. 26.4%,  $\chi^2 = 4.1$ ,  $P = .04$ ). The SGA A group had significantly higher BMI ( $28.9 \pm 6.3$  kg/m<sup>2</sup>) compared with the SGA B and C group ( $23.1 \pm 3.7$  kg/m<sup>2</sup>),  $P < .0001$ . It is important to note that 24.5% of overweight or obese patients (BMI:  $\geq 26$  kg/m<sup>2</sup>) were rated as malnourished



**Figure 1.** Adjusted survival curves for SGA evaluated at the start of dialysis. SGA, subjective global assessment: A = well nourished, B&C = malnourished.

(SGA B and C) and within the malnourished group (SGA B and C) 21% of patients were overweight or obese (BMI:  $\geq 26$  kg/m<sup>2</sup>).

When the combined effects of SGA and BMI were examined, after adjusting for all other variables, the SGA = B and C + BMI:  $\geq 26$  kg/m<sup>2</sup> group was associated with an almost 3-fold increase in mortality risk (HR, 2.96; 95% CI, 1.12 to 7.33;  $P = .02$ ) compared with SGA = A + BMI  $< 26$



**Figure 2.** Adjusted survival curves of the combined effects of SGA and BMI evaluated at the start of dialysis. Note: Group 1 versus 2 ( $P = .73$ ), group 1 versus 3 ( $P = .19$ ), group 1 versus 4 ( $P = .02$ ), group 2 versus 3 ( $P = .14$ ), group 2 versus 4 ( $P = .007$ ), group 3 versus 4 ( $P = .07$ ). SGA, subjective global assessment: A = well nourished, B&C = malnourished; BMI, body mass index in kg/m<sup>2</sup>.

kg/m<sup>2</sup> group (referent) (Fig. 2), although the mean BMI of the SGA = B and C + BMI  $\geq 26$  kg/m<sup>2</sup> group was significantly higher than the SGA = A + BMI  $< 26$  kg/m<sup>2</sup> group ( $28.4 \pm 1.9$  vs.  $23.2 \pm 2.2$  kg/m<sup>2</sup>,  $P < .0001$ ). The SGA = B and C + BMI  $\geq 26$  kg/m<sup>2</sup> group had an almost 2-fold higher mortality risk (HR, 1.77; 95% CI, 0.95 to 3.30;  $P = .07$ ) compared with the SGA = B and C + BMI  $< 26$  kg/m<sup>2</sup> group despite a significant higher mean BMI of  $28.4 \pm 1.9$  kg/m<sup>2</sup> versus  $21.8 \pm 2.8$  kg/m<sup>2</sup>,  $P < .0001$ . This means, among the malnourished groups, those overweight or obese tended to perform worse.

When the combined effects of SGA and s-albumin were examined (Fig. 3), no statistical difference in mortality risk was observed between the SGA = A + s-albumin  $\geq 3.3$  g/dL or SGA = A + s-albumin  $< 3.3$  g/dL group (HR, 1.25; 95% CI, 0.65 to 2.45;  $P = .51$ ), although the latter had significantly lower level of s-albumin ( $3.5 \pm 0.2$  vs.  $2.9 \pm 0.4$  g/dL,  $P < .0001$ ). In comparison with SGA = A + s-albumin  $\geq 3.3$  g/dL group (referent), the SGA = B and C + s-albumin  $\geq 3.3$  g/dL group was associated with a 2-fold (HR, 2.06; 95% CI, 1.06 to 4.00;  $P = .03$ ) increase in mortality risk despite no difference in s-albumin levels ( $3.5 \pm 0.2$  vs.  $3.5 \pm 0.3$  g/dL,  $P < .90$ ). Among the SGA B and C groups with s-albumin  $\geq 3.3$  g/dL or  $< 3.3$  g/dL, no statistical difference in mortality risk ( $P = .26$ ) was observed despite

the statistical difference in s-albumin levels ( $3.5 \pm 0.3$  vs.  $2.8 \pm 0.3$  g/dL,  $P \leq .0001$ ). An almost 3-fold increase in mortality risk was observed for SGA = B and C + s-albumin  $< 3.3$  g/dL group compared with the SGA = A + s-albumin  $\geq 3.3$  g/dL group (HR, 2.86; 95% CI, 1.66 to 4.94;  $P \leq .0001$ ).

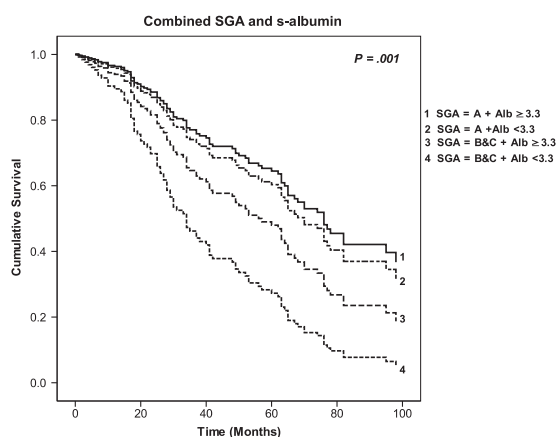
There was no statistical difference in mortality risk among any combinations of s-albumin ( $<$  or  $\geq 3.3$  g/dL) and BMI ( $<$  or  $\geq 26$  kg/m<sup>2</sup>) categories ( $P = .53$ ).

In summary, after adjusting for all variables, including age, gender, dialysis modality, GFR level at which dialysis started, s-albumin levels, BMI, malnutrition score (SGA B and C), smoking, and all co-morbidities, advanced age ( $> 65$  years;  $P < .0001$ ), presence of PVD ( $P < .0001$ ), reduced s-albumin levels ( $P = .01$ ), and malnutrition scored as SGA B and C ( $P = .02$ ) independently predicted mortality. Combined effects of SGA A with BMI  $< 26$  kg/m<sup>2</sup> or s-albumin  $\geq 3.3$  g/dL were associated with better survival.

## Discussion

Our cohort represented a relatively homogeneous group of ESKD patients who showed an uneventful but gradual decline of renal function with no history of AKI and RRT. We observed a high prevalence (52.1%) of malnutrition (SGA B and C) at the start of dialysis. Malnutrition, together with advanced age, reduced s-albumin levels, and presence of PVD independently predicted mortality during the 10-year study period. Gender, dialysis modalities, GFR level at which dialysis was commenced, BMI, positive smoking history, and comorbidities other than PVD did not show any statistically significant effect on mortality risk.

In search of the optimal timing for when dialysis should start, the IDEAL trial<sup>37</sup> compared the mortality between early- (10 to 14 mL/minutes/1.73 m<sup>2</sup>) and late-start (5 to 7 mL/minutes/1.73 m<sup>2</sup>) groups. The mean GFR of the early- and late-starting group resulted at 12.0 mL/minutes/1.73 m<sup>2</sup> and 9.8 mL/minutes/1.73 m<sup>2</sup>, respectively, in the study because of various clinical and social decisions. No statistical difference in survival or clinical outcomes was observed between the early- or late-starting groups. Our cohort study, which included patients with a wider range of clinical implications, also showed no difference in mortality risk when the analyses



**Figure 3.** Adjusted survival curves of the combined effects of SGA and s-albumin evaluated at the start of dialysis. Note: Group 1 versus 2 ( $P = .51$ ), group 1 versus 3 ( $P = .03$ ), group 1 versus 4 ( $P < .0001$ ), group 2 versus 3 ( $P = .16$ ), group 2 versus 4 ( $P = .004$ ), group 3 versus 4 ( $P = .26$ ). SGA, subjective global assessment: A = well nourished, B&C = malnourished; Alb, s-albumin in g/dL.

were performed at the GFR cutoff of 7 mL/minutes/1.73 m<sup>2</sup>, as initially planned in the IDEAL trial, or at the cutoff of 8, 9, and 10 mL/minutes/1.73 m<sup>2</sup>. Our results supported the recommendations of the IDEAL trial and other observational studies<sup>35,44</sup> that with careful clinical management of ESKD, including nutritional inputs, dialysis can be started at lower levels of GFR (<7 mL/minutes/1.73 m<sup>2</sup>).<sup>34,45</sup> In agreement with the literature, we found no significant difference in mortality risk between HD and PD.<sup>28,42</sup> This suggests patients should be able to start on either modalities based on their clinical and psychosocial needs when the time is right.

The effects of hypoalbuminemia on mortality have been inconsistent in the literature<sup>46-48</sup> because of reasons such as the presence of inflammation (duration and magnitude) and duration and the severity of hypoalbuminemia. The present study indicated that s-albumin levels were an independent predictor of mortality. This result was consistent with the findings of a number of studies,<sup>23,47,49,50</sup> but differed from others.<sup>28,48,51</sup> In the latter studies, the predictive effect of s-albumin was ameliorated after adjusting for CRP, and this may be a limitation of our study because CRP was not routinely measured. Therefore, the independent predictive effect of s-albumin as solely nutritional could not be concluded. However, we did consider for other study variables, including the known associates of inflammation such as history of AKI, surgery (PD catheter insertion), obesity, and other comorbidities. Thus, it is reasonable to speculate the strong role of poor nutrition or type I malnutrition caused by a reduced protein and energy intake<sup>2</sup> plays in the predictive effect of s-albumin levels in our study, similar to other reports in the literature.<sup>19,29</sup>

Similar to previous findings, the SGA rating of malnutrition was found to be an independent predictor of mortality.<sup>28,49,52</sup> A sustained reduction of dietary intake is a major determinant of SGA rating, and as we considered sustained intakes of protein and energy of less than 80% of requirements as inadequate, it was reasonable to deduce that the predictive effect of low s-albumin levels constituted a significant nutrition component. It is possible that both type I and type II malnutrition coexist with nutritional and inflammatory factors compounding the effects on each other, and their significance cannot be mutually exclusive. We did not examine the effect of the individual compo-

nents of SGA on survival, but it is known that these individual components reflect long-term changes and are highly predictive of mortality and morbidities, such as unintentional weight loss,<sup>19,53</sup> reduced dietary intake,<sup>50,54,55</sup> poor appetite,<sup>26,56</sup> and muscle wasting.<sup>57</sup> Our study supports the use of SGA score at the start of dialysis as a powerful independent predictor of survival, as previously reported by other researchers.<sup>28,49,52</sup>

In contrast to the literature,<sup>28,49,50</sup> diabetes was not observed to be associated with higher mortality risk in our study. This may be explained by a higher proportion of our patients with diabetes being well nourished, possibly counteracting the effects of the uremic wasting on mortality over time. Our results were similar to those of the Dialysis Outcomes and Practice Patterns Study (DOPPS)<sup>58</sup> which reported diabetic patients had significantly lower odds of cachectic appearance than nondiabetic patients. Cardiovascular disease was found to be an independent predictor of mortality in several studies.<sup>28,49,59</sup> We found CAD to be significant in the unadjusted analyses, but the significance disappeared in the adjusted analyses (HR, 1.45; 95% CI, 0.94 to 2.19; *P* = .10). This can possibly be explained by the unknown duration and severity of cardiovascular conditions in our cohort. Also, our patients were much older (mean age, 65.3 ± 13.6 years compared with 50 to 56 years in these studies), and the age factors may explain some of the variation in our findings. Other reasons could be the varied observational periods or the heterogeneity of uremia-related nutritional effects before starting dialysis in previous studies. Such reasons include unplanned initiation of dialysis because of unforeseen events (e.g., AKI caused by infections and surgical complications), duration of malnutrition, and previous transplantation. It is not clear whether dialysis was initiated for the same reasons in all patients in reported studies.

The obesity paradox<sup>32,33,60,61</sup> has created much debate in the renal community regarding the protective effect of obesity in ESKD patients. A recent systematic review<sup>62</sup> of the relationship between BMI and mortality supported the inverse association between BMI and all-cause mortality in adult (HD) patients, especially in elderly patients. In other studies,<sup>50,63,64</sup> it has been argued that when body composition was also considered, the possible protective effect of high BMI is limited to subjects with normal and high muscle mass

only. Similarly to previous findings,<sup>31,65</sup> our study revealed being overweight or obese was not found to have any protective effects, and when combining with malnutrition scores, it was associated with the worst outcome. Our findings echoed the high mortality risk found in those with obese sarcopenia.<sup>66</sup> In addition, the combined effects SGA A and BMI <26 kg/m<sup>2</sup> were found to have the best survival advantage. Again, higher BMI did not show protective effects with either low or normal levels of s-albumin. Most importantly, being well nourished (SGA A) was found to be associated with lower mortality risk irrespective of the levels of s-albumin and BMI. Our study highlighted the usefulness of the combined effects of nutritional parameters in predicting outcomes.

There are limitations to our study. The main ones are the lack of measurement of inflammatory biomarkers (CRP), small sample size, and unknown duration and severity of lifestyle factors such as smoking history and comorbidities (e.g., CAD). We also did not measure the effect of nutrition interventions before and after dialysis initiation. Patients may respond to nutritional management differently depending on the type, severity, and duration of their nutritional issues, and the degree of exposure to intervention. Our study points to the need for timely access to structured nutritional care to prevent and manage nutritional abnormalities well before dialysis is required, and if it is required, to help maintain nutrition status on the conservative management pathway.

The strength of this study is the long follow-up time in a well-defined cohort of patients experiencing relatively homogeneous nutritional effects before dialysis started. It is a good example of how informative research can be conducted within the practice of renal care.

## Conclusions

In the study reported here, a high prevalence of malnutrition among patients with ESKD at the initiation of dialysis was observed. During a 10-year period, advanced age (>65 years), reduced s-albumin levels, presence of PVD, and malnutrition scores were found to independently predict mortality. Other studied factors, such as gender, dialysis modality, GFR level at which dialysis was initiated, BMI, positive smoking history, and presence of all other comorbidities, were not

found to be associated with higher mortality risk. A high BMI was not associated with any survival advantage, and when combined with the presence of malnutrition, it was associated with the highest mortality risk. The combined effects of these simple readily available nutritional parameters were effective in predicting mortality independently and are highly informative for practice management and evaluation.

## Practical Application

Malnutrition scored by SGA (B and C) at the start of dialysis was associated with high mortality risk irrespective of the BMI and s-albumin levels. Being overweight or obese did not show any protective effect and was associated with the worst outcome with the presence of malnutrition. These findings suggest nutrition intervention to optimize nutritional status should be considered in patients with ESKD well before dialysis is required.

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